REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the final Office Action dated January 27, 2006 (hereinafter, "the Final Action") and the Advisory Action dated May 3, 2006 (hereinafter, "the Advisory Action"). Claims 12, 15, 19-21, 24-26 and 31-35 are pending in the present application upon entry of the present Amendment Accompanying Request for Continued Examination. The concerns raised by the Examiner in the Final Action are addressed below.

I. Interview Summary

Applicants again wish to express their appreciation to the Examiner for the courtesy call extended to Applicants' legal representative, Shawna Cannon Lemon, indicating the issuance of the Final Action upon consideration of the Applicants' response dated October 31, 2005. In view of this courtesy call and further in view of the Final Action and the Advisory Action, Applicants provide the following remarks to address the specific concerns regarding the obviousness, anticipation, enablement and indefiniteness rejections.

II. Claim Rejections Under 35 U.S.C. § 103

Claims 12, 15, 19-21, 23-26 and 31-35 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Bukowski et al. *Blood.* **84** (No. 1, Suppl. 1): 129a (1994) (hereinafter, "Bukowski et al.") for reasons set forth in the current Final Action and the paper mailed June 30, 2005, Section 4, pages 2-3. *See* Final Action, page 2.

Applicants reiterate that (a) the method of the cited reference does not teach or suggest the same methods recited in the pending claims, and (b) the method discussed in the cited reference would not inherently lead to enhanced suppression of endothelial growth associated with administration of a chemotherapeutic agent, for example, cisplatin. As previously noted, and further explained in detail in the previously submitted Declaration Under 37 C.F.R § 1.132 of George Sigounas, Ph.D. (hereinafter, the "Sigounas Declaration"), cancer patients typically do not receive EPO **prior to** initiation of chemotherapy. Accordingly, before Applicants' discovery, there was **no** motivation to provide EPO to cancer patients other than to treat anemia, and to treat anemia only **after** initiation of chemotherapy.

In order to clarify the methods recited in the pending claims, Applicants have amended Claims 12 and 21 to include the recitation "prior to **initial** administration of a chemotherapeutic agent" (Claim 12) and "prior to **initial** administration of cisplatin" (Claim 21) (Emphasis added). Applicants respectfully submit that support for these claim amendments can be found in the specification and drawings as originally filed. More specifically, Applicants respectfully submit that, upon a fair reading of the specification, a person of ordinary skill in the art would recognize in the present disclosure that the timing of EPO administration "prior to" administration of a chemotherapeutic agent or administration of cisplatin conveys administration prior to the initiation, *i.e.*, before the first dose, of chemotherapy. As demonstrated in the specification, and as further supported by way of the Sigounas Declaration, EPO can increase the susceptibility of a solid vascularized tumor to a chemotherapeutic agent and/or cisplatin when EPO is administered before administration of the particular agent. Turning specifically to the specification, Figure 4 presents a graph showing the responses of endothelial cell cultures exposed first to varying dosages of EPO and, two hours later, to cisplatin (compared to control endothelial cell culture exposed only to cisplatin). Clearly, EPO was provided to the cells prior to **any** previous exposure of the cells to cisplatin. The Sigounas Declaration provides *in vivo* data that supports the disclosure of the specification as originally filed. Accordingly, the *in vitro* data presented in the specification sets forth the protocol for administering EPO to patients prior to the **initial** administration of a chemotherapeutic agent and/or cisplatin for the treatment of solid vascularized tumors. These observations are indeed commensurate in scope with the claimed invention.

Moreover, Applicants respectfully assert that, upon application of the appropriate standard for evaluating patent claims for adequate written description, it is apparent that the claims of the present invention meet this requirement. A review of the case law reveals that the courts have consistently held that it is well established that there is no *in haec verba* requirement and that newly added claim limitations can be supported in the specification through **express, implicit, or inherent disclosure**. *See* "Written Description" Requirement as published on January 5, 2001 in the Federal Register (Vol. 66, pages 1099-1111), page 1105, first column of the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 (Emphasis Added). Moreover, the Court of Customs and Patent Appeals

(CCPA) has stated that "[t]he function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter now claimed by him; how the specification accomplishes this is not material . . . . It is not necessary that the application describe the claim limitations exactly . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that applicants invented processes including those limitations." (*In re Wertheim*, 541 F.2d 257 (CCPA 1976), citing *In re Smith*, 482 F.2d 910 (CCPA 1973) and *In re Smythe*, 480 F.2d 1379 (CCPA 1973).

Lastly, the Final Action states that "the Sigounas Declaration is not commensurate in scope with the claimed invention since, in the animal model presented, only 60 Units per kilogram were administered prior to administration of the chemotherapeutic agent (see p. 4 of the Declaration)." Final Action, page 3. Applicants note that the dosage used in the studies referenced in the Final Action was 60 Units per **mouse**. 60 Units per mouse corresponds to approximately 2000 Units per kilogram. Thus, Applicants respectfully submit that the data provided in the Sigounas Declaration are commensurate in scope with the pending claims.

Accordingly, Applicants respectfully submit that Claims 12, 15, 19-21, 23-26 and 31-35 are not obvious in view of Bukowski et al., and Applicants respectfully request withdrawal of these claim rejections.

III. Claim Rejections Under 35 U.S.C. §102

Claims 12, 15, 19-21, 23-26 and 31-35 stand rejected under 35 U.S.C. §102(b) as being unpatentable over Bukowski et al. for reasons previously set forth in the current Final Action and the paper mailed June 30, 2005, Section 5, pages 3-7. *See* Final Action, page 5.

Anticipation requires that each and every element of the claim is found in a single prior art reference. *W. L. Gore & Associates Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983). However, a finding of anticipation also requires that there must be no difference between the claimed invention and the disclosure of the cited reference as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). Additionally, the cited prior art reference must be enabling, thereby placing the allegedly disclosed matter in the possession of the public. *In re Brown*, 329 F.2d 1006, 1011,

141 U.S.P.Q. 245, 249 (C.C.P.A. 1964).

As noted above, Applicants have amended Claims 12 and 21 to include recitations directed to administration prior to "initial" administration of a chemotherapeutic agent and/or cisplatin. Bukowski et al. is directed to treatment of anemic cancer chemotherapy patients, *i.e.*, patients who have received a chemotherapeutic agent **before** receiving EPO treatment. Thus, Bukowski et al. does not teach or suggest the recited methods.

Applicants further note that it is well-established that the proper test of a publication as a §102(b) bar is "whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought." *In re Elsner*, 381 F.3d 1125, 1128, 72 U.S.P.Q.2d 1038 (Fed. Cir. 2004) (*quoting In re LeGrice*, 301 F.2d 929, 939 (C.C.P.A. 1962)). Accordingly, "[e]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Helefix Limited v. Blok-Lok, LTD*, 208 F.3d 1339, 1347, 54 U.S.P.Q.2d 1299 (Fed. Cir. 2000) (*quoting In re Donohue* 766 F.2d 531, 226 U.S.P.Q 619,621 (Fed. Cir. 1985)). Applicants respectfully submit that Bukowski et al. is not an enabling reference and one skilled in the art would not be in possession of the present invention on the basis of combining one's own knowledge with the disclosure presented in Bukowski et al.

Whether a prior art reference is enabling is a question of law based upon underlying facts. *See SmithKline Beecham Corp. v. Apotex Corp.* 403 F.3d 1331, 1342-1343, 74 U.S.P.Q. 2d 1398 (Fed. Cir. 2005) (*citing Crown Operations Int'l Ltd. v. Solutia, Inc.* 289 F.3d 1367, 1376 (Fed. Cir. 2002)). In this instance, as noted above, Bukowski et al. is directed to treatment of anemia in cancer patients who receive EPO **after** administration of chemotherapy in order to treat the resulting anemia. Based upon this disclosure, one skilled in the art would not be apprised as to a method of treating solid vascularized tumors as recited in the pending claims. In further support of this conclusion, Applicants submitted the Sigounas Declaration that shows that before to the present invention, those of skill in the art would **not** administer EPO before treatment with chemotherapeutics, but alternatively, the skilled artisan would only administer EPO **following** the diagnosis of anemia. Clearly, Bukowski et al. fails to provide an enabling disclosure to treat a solid vascularized tumor in a

subject in need of such treatment, comprising administering erythropoietin prior to **initial** administration of a chemotherapeutic agent or cisplatin, wherein said erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of said chemotherapeutic agent or cisplatin.

Accordingly, at least in view of the foregoing, Applicants respectfully submit that the pending claims are not anticipated by Bukowski et al., and Applicants respectfully request that these claim rejections be withdrawn.

IV. Claim Rejections Under 35 U.S.C. §112, First Paragraph

Claims 12, 19-21, 23-26 and 31-35 stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. *See* Final Action, page 5. More specifically, the Office Action states that "the specification, while being enabling for the claimed method wherein the claimed chemotherapeutic agent is cisplatin, does not reasonably provide enablement for the claimed method with administration of a chemotherapeutic agent." Final Action, page 5. Applicants respectfully disagree with this assertion.

Applicants have, however, amended Claim 15 to recite that the chemotherapeutic agent is "selected from the group consisting of cisplatin, carboplatin and mitomycin," and Applicants have amended Claim 21 to recite that the chemotherapeutic agent is "cisplatin." Support for these claim amendments can be found in the specification as originally filed, for example, page 10, lines 16 and 17.

Regarding Claim 12, the Final Action further states that "[g]iven the information in the Declaration and in the instant response, it appears that it cannot be predicted if any chemotherapeutic activity other than CIS, can be potentiated by the prior administration of EPO or how to use the claimed invention if it does not potentiate the effects of the chemotherapeutic agent." Final Action, page 7. Applicants respectfully submit that the data show that EPO can modulate tumor response to chemotherapy. In a particular study discussed in the Sigounas Declaration, a reduction in tumor mass resulted from the sequential administration of EPO and mitomycin. Although, as noted in the Final Action and the Advisory Action that this difference was not statistically significant, Applicants respectfully submit that the data nevertheless show that EPO can modulate tumor response to chemotherapy where a notable reduction in tumor response was shown in the experiments

discussed therein. Applicants respectfully submit that there is no legal requirement for enablement that the distinct difference shown in the experiments be "statistically significant." Applicants are aware that the question of statistical significance was considered by the Court of Customs and Patent Appeals in *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), in interpreting the utility requirement under 35 U.S.C. §101. In *Nelson*, the court explicitly rejected the argument that "confirmation by statistically significant means" was required to meet the utility requirement. *Id.* at 883. The court, instead, stated that the pharmacological activity need only be "reasonably indicative of the desired response." *Id.* at 884. Applicants respectfully submit that results discussed in the Sigounas Declaration meet the level of providing a reasonable indication of a reduction in tumor mass as a result of sequential administration of EPO and mitomycin and that no further statistical significance should be required.

The "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (M.P.E.P. §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Applicants respectfully submit that the reasonably skilled physician would be able to treat a patient by administering EPO prior to **initial** administration of a chemotherapeutic agent or a chemotherapeutic agent selected from the group consisting of cisplatin, carboplatin and mitomycin through routine medical practice. In particular, it is routine within the medical field to administer various therapeutic agents to a patient until the desired therapeutic effect is achieved. Thus, it would not be an undue burden, but rather routine, for the reasonably skilled physician to administer EPO prior to initial administration of a chemotherapeutic agent other than cisplatin in order to treat a solid vascularized tumor as recited in the pending claims.

Applicants respectfully submit that the specification, coupled with the knowledge and customary medical practice of one skilled in the art, enables one reasonably skilled in the art to make and use the present invention without undue experimentation. Accordingly, Applicants respectfully submit that the pending claims are enabled, and Applicants respectfully request that these claim rejections be withdrawn.

V. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

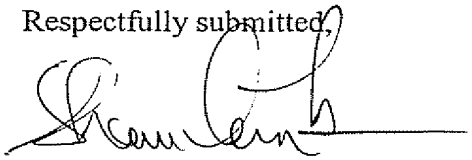
Claims 23 and 24 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. *See* Final Action, page 8.

Applicants have canceled Claim 23 and amended Claim 21 so that antecedent basis is provided for the recitation "said cisplatin" in Claim 24. Accordingly, Applicants respectfully request that these claim rejections be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,



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